Patent Certification Under 21 CFR §314.94 and Notice of Certification of Invalidity or Noninfringement of a Patent Under 21 CFR §314.95

I. Andrx Labs, L.L.C. (Andrx), having a place of business at 4955 Orange Drive, Davie, Florida 33314, hereby certifies to the following persons that it has filed a New Drug Application under 21 U.S.C. §505(b)(2) for permission to sell Sodium Valproate Delayed-release Tablets, 500 mg Valproic Acid activity that are bioequivalent to Depakote® 500 mg valproic acid activity tablets; Sodium Valproate Delayed-release Tablets, 250 mg valproic acid activity that are bioequivalent to Depakote® 250 mg valproic acid activity tablets; and Sodium Valproate Delayed-release Tablets, 125 mg valproic acid activity that are bioequivalent to Depakote® 125 mg valproic acid activity tablets:

A. Holder of New Drug Application for Depakote®

Abbott Laboratories
100 Abbott Park Road
Abbott Park IL 60064

B. On information and belief the owner of U.S. Letters Patent Nos. 4,988,731 and 5,212,326 is:

Abbott Laboratories
100 Abbott Park Road
Abbott Park IL 60064

II. The United States Food and Drug Administration has received a New Drug Application (NDA) from Andrx which contains bioequivalence data which shows that each of Andrx' Valproate Sodium Delayed-Release Tablets, 500 mg valproic acid activity, 250 mg valproic acid activity, and 125 mg valproic acid activity, are bioequivalent to the respective strengths of Depakote® tablets. A Paragraph IV Certification under 21 CFR §314.94 was submitted with the NDA.

III. The Andrx New Drug Application Number is 21-617.

IV. The established names for the proposed drug products are Sodium Valproate Delayed-release Tablets, 500 mg Valproic Acid activity; Sodium Valproate Delayed-release Tablets 250 mg Valproic Acid activity, and Sodium Valproate Delayed-release Tablets 125 mg Valproic Acid activity.

V. The active ingredient for the proposed drug products is valproic acid; the dosage forms are oral tablets that will be sold in 500-mg valproic acid activity strengths, 250-mg valproic acid strengths, and 125-mg valproic acid strengths.

VI. The following patents (the "listed patents") which have been listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "*Orange Book*") are known to Andrx and will either (a) not be infringed by the making, using, or selling of Andrx' Sodium Valproate Delayed-release Tablets 500 mg valproic acid activity, Sodium Valproate Delayed-release Tablets 250 mg valproic acid activity, and Sodium Valproate Delayed-release Tablets 125 mg valproic acid activity products (Andrx' Proposed Products); or (b) be invalid and/or unenforceable if the claims are asserted to read on Andrx' Proposed Products:

U.S. Patent No.	Expiration Date
4,988,731	January 29, 2008
5,212,326	January 29, 2008

A copy of each of these patents is attached hereto as an Appendix.

VII. The above U.S. patents, which have been listed in the Orange Book will not be infringed by Andrx' Proposed Products or, in the alternative, would be invalid or unenforceable against Andrx' Proposed Products for a number of reasons which are described below:

The listed patents will not be infringed by Andrx' Proposed Products because the claims of those patents concern particular oligomeric compositions or oral pharmaceutical dosage forms containing those oligomeric compositions which are completely different from Andrx' Proposed Products. To summarize:

- Andrx' Proposed Products are not, and do not contain, the claimed oligomeric form which is divalproex sodium. Therefore, Andrx' Proposed Products do not fall within the literal scope of the claims of the '731 or '326 patents. Neither do Andrx' Proposed Products contain the monomer of the complexed sodium valproate:valproic acid in a 1:1 ratio. Therefore, Andrx' Proposed Products do not contain any form of divalproex sodium that would infringe the listed patents under the doctrine of equivalents.

- The doctrine of equivalents cannot be applied to Andrx' Proposed Products because Andrx' Proposed Products contain a compound which is in the prior art, namely sodium valproate. The scope of the claims of the '731 and '326 patents cannot be expanded to cover prior art (including Andrx' Proposed Products) because patent protection cannot be afforded to that which is in the public domain. Accordingly, Andrx is free to use the prior art (public domain) non-oligomeric form of divalproex sodium, namely sodium valproate, without infringing either of the '731 or '326 patents.

- Because Andrx' Proposed Products contain a prior art compound as their active ingredient, any allegation that the '731 or '326 patents are infringed by Andrx' Proposed Products would necessarily mean that the claims of these listed patents read on the prior art. Any assertion that Andrx' Proposed Products infringe the claims of the listed patents would be an improper use of the listed patents. Thus, the '731 and '326 patents are either invalid or are unenforceable against Andrx' Proposed Products which employ sodium valproate, i.e., a non-oligomeric and non-complexed form of divalproex sodium.

The distinctions which differentiate Andrx' Proposed Products from the claims of the listed patents are detailed below:

United States Patent No. 4,988,731

The claims of U.S. Patent No. 4,988,731 (the '731 patent) specifically require an oligomer comprising about four (4) units of complexed sodium valproate and valproic acid in a 1:1 ratio. The '731 patent contains two claims, both of which are reproduced below:

1. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$), and containing about 4 such units.

2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$), and containing about 4 such units.

Andrx' Proposed Products do not contain the claimed oligomer. Nor do Andrx' Proposed Products contain the monomer of complexed sodium valproate/valproic acid in a 1:1 ratio.

The initial manufacturing step for Andrx' Proposed Product, utilizing divalproex sodium, is performed outside the United States and outside any United States territories subject to United States patent laws. This initial formulation step involves adding excess sodium hydroxide solution to divalproex sodium, thereby resulting in a high pH solution (pH 10.8, 50% w/w) which contains non-oligomeric, non-complexed sodium valproate. This high pH for the solution (termed "sodium divalproate pH-adjusted solution") is maintained throughout the manufacturing process; thus, the oligomeric form is forever destroyed. The sodium valproate in pH-adjusted solution is then shipped into the United States where the sodium valproate pH-adjusted solution is diluted with alcohol and sprayed onto anhydrous lactose to form a granulation. This granulation is then tableted, and coated with cellulose acetate phthalate.

The sodium valproate pH-adjusted solution imported into the United States contains no trace of the patented divalproex sodium oligomer, nor does it contain the divalproex sodium monomer at any stage of the wet granulation or tableting process. Therefore Andrx' formulation cannot literally infringe any valid claim of the '731 patent.

The specification of the '731 patent recites several properties that are characteristic of the oligomeric divalproex sodium and, therefore, can be used to identify the claimed oligomer or complex. These properties include NMR spectra, mixed melting-point determination, IR spectra, and X-ray diffraction. See '731 patent at col. 2, lines 14-16. In addition, the claimed oligomer is described as a crystalline, stable solid which has the advantage of being non-hygroscopic. Independent testing of Andrx' Proposed Products clearly establishes that the oligomeric form of divalproex sodium is completely absent at all stages of the manufacturing process that occur within the United States.

Using these and other assays, side-by-side comparison of the claimed oligomer in solution, in powder form, and as final product with analogous forms used in Andrx' Proposed Products confirms that Andrx' Proposed Products do not contain the claimed oligomer. From the data resulting from these comparative tests, it is conclusive that Andrx' Proposed Products use the prior art compound, sodium valproate. The results of these comparative assays are summarized below and are fully presented in the attached Exhibit A.

Summary of Characterization Test Results for Andrx' Proposed Product v. Patented Product

Test	Solution (50% w/w)		Granulation Material		Finished Product	
	sodium valproate pH-adjusted solution	Patented Divalproex sodium oligomer (solution)	Andrx Proposed Product Granulation	Patented Divalproex sodium oligomer	Andrx' Proposed Products	Depakote® (500 mg tablet)
pH	10.8	7.1	—	—	6.7	4.6
Infrared Peak near 1685 cm^{-1} ?	No	Yes (1707)	No	Yes (1696)	No	Yes (1701)
Melting Point (EC)	—	—	>152	~100	—	—
Hygroscopicity*	—	—	2.9	0.1	2.1**	0.4**
X-ray Diffraction (°/2θ)	—	—	5.9, 6.9	7.3	5.75, 6.8	7.2

* Measured as % weight gain after 45 minutes at room temperature (80% rel. humidity)
** Tablet core material

As shown in the above table, Andrx' Proposed Products are clearly distinct from the claimed oligomeric compound of the '731 patent. Specifically, the sodium valproate pH-adjusted solution used in the preparation of Andrx' Proposed Products has a pH of 10.8. This is significantly higher than the pH of 7.1 measured for the patented divalproex sodium oligomer in solution at an identical concentration. The high pH for the solution used in the manufacture Andrx' Proposed Products completely disrupts and forever destroys the claimed oligomeric form. Neither can the monomer exist at this high pH. The pH measurements for the final formulated tablets of Andrx' Proposed Products is also much higher than the Depakote® tablets.

The IR spectra for Andrx' Proposed Products further illustrate their distinction from the claimed oligomeric divalproex sodium. A distinctive peak at about 1685 cm^{-1} is identified in the IR spectra for the patented divalproex sodium oligomer. This distinctive peak is consistently present in solution, in the active ingredient (drug substance), and in the final Depakote® product. The distinctive divalproex sodium peak is completely absent in Andrx' Proposed Products (solution, granulation, and final product). The IR spectra for Andrx' Proposed Product mimics that of the prior art compound, sodium valproate (see Exhibit A).

Moreover, Andrx' Proposed Products have a melting point much higher than the patented oligomer. Andrx' Proposed Products showed no physical change between 180°C and 400°C (the upper limit of the melting point apparatus). The claimed oligomer is recited as having a melting point range of 98-100°C, which was confirmed by Andrx' tests.

Another distinctive characteristic of Andrx' Proposed Products is that they are hygroscopic. The non-hygroscopic property of the claimed oligomer was relied on by the patentee of the '731 patent to establish a patentable distinction from the compounds in the prior art (see '731 patent, col. 2, lines 25-26 and lines 58-61). Thus, the hygroscopicity of Andrx' Proposed Products illustrates its similarity to the prior art compounds and supports the position that they fall outside the claims of the '731 patent, both literally and under the doctrine of equivalents.

Finally, the X-ray diffraction pattern exhibited by Andrx' Proposed Products is clearly different from the X-ray diffraction pattern exhibited by the patented oligomers. The distinctive pattern for Andrx' Proposed Products shows a doublet peak at 5.75-5.9 and 6.8-6.9 units, whereas the patented oligomer does not exhibit the doublet peak. Instead, the patented oligomer exhibits a single peak at about 7.5 units. The X-ray diffraction pattern is a strong indication that Andrx' Proposed Product is a completely different compound from the patented oligomer.

In view of these side-by-side tests, Andrx' Proposed Products are shown to be distinct, and therefore do not literally infringe the claims of the '731 patent.

Further, Andrx' formulation cannot infringe any valid claim of the '731 patent under the doctrine of equivalents. Both the specification and the prosecution history of the '731 patent admit that sodium valproate and valproic acid are known prior art compounds that have been used for the treatment of epileptic seizures and convulsions. Additionally, valproic acid and valproic acid salts, such as sodium salts, have long been known to be useful in the treatment of epileptic seizures and convulsions. See generally, United States Patents Nos. 4,261,974 and 4,292,425, 4,301,176 and 4,323,507. Therefore, because Andrx imports into the United States sodium valproate pH-adjusted solution which contains the prior art, non-oligomeric sodium valproate, and this compound is employed at all stages of the formulation process for Andrx' Proposed Products, the claims of the '731 patent cannot be expanded under the doctrine of equivalents to include Andrx' Proposed Products.

Finally, it is noted that the '731 patent fails to contain any claims that recite a process for forming the claimed oligomer or pharmaceutical formulation containing the claimed oligomer. Accordingly, there can be no valid claim of infringement of the '731 patent under 35 U.S.C. § 271(g).

United States Patent No. 5,212,326

U. S. Patent No. 5,212,326 (the '326 patent) which is a continuation of the '731 patent discussed above, also provides protection only for the oligomeric form of the sodium valproate-valproic acid complex (termed "divalproex"). The broadest claims from the '326 patent are reproduced below:

> 1. An oligomer having a 1:1 molar ration of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H)$ and containing about 4 to 6 such units.
>
> 2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H)$, and containing about 4 to 6 units.
>
> 3. An oligomer having a 1:1 molar ration of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H)$ and containing about 6 such units.

4. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$), and containing about 6 such units.

5. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$), and having physical/chemical properties as follows: (a) stable, white crystalline powder; (b) melting point of 98° to 100°C; and (c) an infrared spectrum having strong absorption bands at about 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1}.

Claims 1-4 of the '326 patent require an oligomer comprising from 4 to 6 units of sodium valproate and valproic acid. Claim 5 of this patent requires an oligomer comprising units of sodium valproate and valproic acid and having specific properties.

Andrx' formulation cannot literally infringe any valid claim of the '326 patent because the valproate sodium pH-adjusted solution that is imported into the United States for preparation of Andrx' Proposed Products does not contain any trace of sodium divalproex oligomer as claimed in the '326 patent. Further, no detectable amount of the sodium divalproex oligomer is present at any stage of Andrx' wet granulation or tablet formation process for Andrx' Proposed Products. See generally, discussion of Andrx' Proposed Product vis-à-vis the '731 patent, above, and the accompanying data. Therefore, the Andrx formulation cannot literally infringe any valid claim of the '326 patent. The melting point and IR spectra of Andrx' Proposed Product do not match the properties listed in claim 5 of the '326 patent. Specifically, the patented oligomer is claimed as a white crystalline powder exhibiting a melting point of 98°-100°C and strong IR bands at 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1}. As detailed in the discussion of non-infringement of the '731 patent, above, and the accompanying data presented in Exhibit A, the melting point for Andrx' Proposed Products is much higher than 98°-100°C and does not exhibit a characteristic IR peak at or near 1685 cm^{-1}

Andrx' formulation also cannot infringe any valid claim of this patent under the doctrine of equivalents. The established knowledge that sodium valproate and valproic acid were used for treating epileptic seizures and convulsions more than one year prior to the filing date of the '326 patent or the related '731 patent remove Andrx' Proposed Products from the scope of equivalents that would be afforded the claims of the '326 patent. The Andrx formulation contains only sodium valproate, a prior art compound. Therefore, the claims of the '326 patent cannot be properly asserted to include the Andrx formulation because the claims would read on the prior art.

Because the '326 patent also fails to contain any claims that recite a process for forming the claimed oligomer or a pharmaceutical formulation containing the claimed oligomer, there can be no valid claim of infringement under 35 U.S.C. § 271(g).

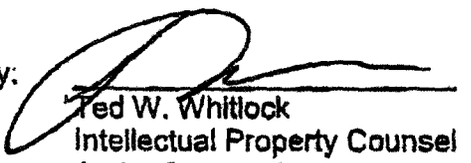
For the above reasons, Andrx' Proposed Products will not infringe any claims in the listed patents.

It is hereby certified that on March 26, 2003, a copy of this Notice has been sent by registered mail, return receipt requested, and by EXPRESS MAIL, return receipt requested, to Abbott as the holder of New Drug Application for Depakote® Tablets and owner of U.S. Patent Nos. 4,988,731 and 5,212,326 in an envelope addressed to:

Abbott Laboratories
100 Abbott Park Road
Abbott Park IL 60064

Respectfully,
Andrx Labs, L.L.C.

March 26, 2003

By: 

Ted W. Whitlock
Intellectual Property Counsel
Andrx Corporation
4955 Orange Drive
Davie, Florida 33314

Exhibit A

Side-by-side comparison of Depakote® v. Andrx' Proposed Product
(Raw Data)

1. **Results of pH Measurement**

Sample[a]	Solution Conc (w/w)[b]	Observation	pH
Andrx valproate sodium solution (pH adjusted to ~11) (Lot # 170R001)	50.0% (As is)	clear solution	10.98
	21.4%	clear solution	9.87
	3.7%	clear solution	7.72
	0.09%	clear solution	5.95
Aqueous Solution of Divalproex Sodium (without pH adjustment)	50.0%	clear solution	7.07
	21.4%	two-layer solution	6.94
	3.7%	two-layer solution	6.05
	0.09%	clear solution	4.75
Aqueous Solution of Sodium Valproate	50.0%	clear solution	9.88
Aqueous Solution of Andrx Granulation	50.0%	stick, cloudy solution	10.22
Aqueous Solution of Anhydrous Lactose	50.0%	cloudy solution	3.79
Aqueous Solution of Andrx Granulation	0.09%	clear solution	6.80
Aqueous Solution of Andrx Core Tablet	0.09%	cloudy solution	6.98
Aqueous Solution of Andrx Finished Product	0.09%	cloudy solution	6.70
Aqueous Solution of Depakote7 Tablet, 500 mg	0.09%	cloudy solution	4.64

Note:

a. A boiled water (pH 7.3) was used to prepared all the solutions, except for Andrx Divalproex Sodium Solution (As is).

b. Concentration was calculated based on valproic acid.

2. **Results of Infrared (IR) Studies**

No	Sample [a]	Peaks (cm^{-1}) [b]
1	Andrx valproate sodium pH-adjusted solution (pH adjusted to ~11) (Lot # 170R001)	2959, 2933, 2873, 1642, 1546, 1379
2	Aqueous Solution of Divalproex Sodium (50%, w/w) (without pH adjustment)	2959, 2935, 2784, 2523 (b), 1955 (b), 1707, 1542, 1380
3	Aqueous Solution of Sodium Valproate (50%, w/w)	2959, 2934, 2874, 1643, 1544, 1379
4	Sodium Valproate (solid)	2958, 2933, 2872, 1570, 1552, 1413
5	Divalproex Sodium (solid)	2960, 2935, 2874, 2509 (b), 1948 (b), 1695, 1570, 1559, 1381
6	Andrx Granulation (Lot # 171R001)	2960, 2932, 2872, 1570, 1559, 1552, 1415
7	Andrx Core Tablet (Lot # 181R001)	2959, 2933, 2873, 1552, 1413
8	Andrx Finished Product, 500 mg (Lot # 184R001)	2959, 2932, 2873, 1641, 1600, 1378
9	Depakote7 Tablet, 500 mg (Lot # 45-404-AA-21)	2960, 2935, 2875, 2560 (b), 1962 (b), 1701, 1686, 1569 1578,1569, 1530, 1385

Note:

a. 1) The solution samples (#1-3) were dispersed between two flat ZnSe plates, whether the solid samples (#4-9) were prepared as KBr pellets.
   2) The spectra of solution samples (#1-3) were subtracted by the spectrum of water.
   3) The coating of samples # 8-9 were removed in sample preparation.

b. Except for those broad peaks indicated by A(b)≅, all peaks listed here are generally sharp.

3. Results of Melting Point Studies

Sample	Physical Observation[a]
Divalproex Sodium (Lot # 9902044)	Sample completely melted 99-100EC
Andrx Granulation (Lot # 171R001)	Sample turned to brownish at ~149EC, melted at ~152EC to yield a dark brown liquid, solidified at ~154EC, and became partially melt at ~185EC.

Note:

a. Each sample was studied three times.

4. Results of Hygroscopicity Studies

A. Andrx Granulation vs. Divalproex Sodium Drug Substance

Sample	Weight Gain (%) @ RT/ 80% RH[a]				
	30 min	45 min	60 min	90 min	120 min
Andrx Granulation[b] (Lot # 171R001)	1.88	2.89	3.64	5.32	6.75
Divalproex Sodium (Lot # 9902044)	0.01	0.04	0.06	0.07	0.09

a. Data were calculated based on n = 2 (duplicate).
b. The potency of Andrx granulation is 69.29% (w/w, in terms of divalproex sodium). The data shown here data were calculated based on the drug substance presented in the sample.

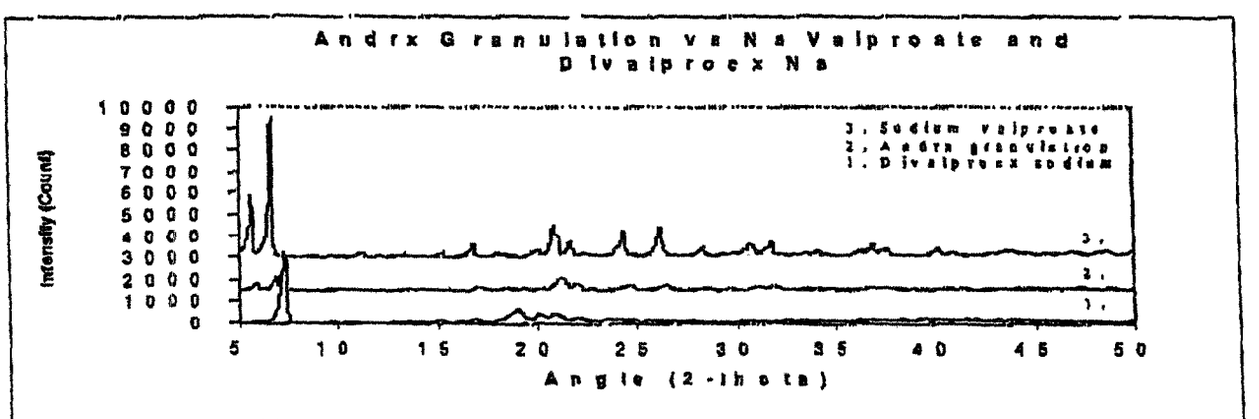
B. Andrx Core Tablets and Finished Products vs. Depakote[7] Tablets

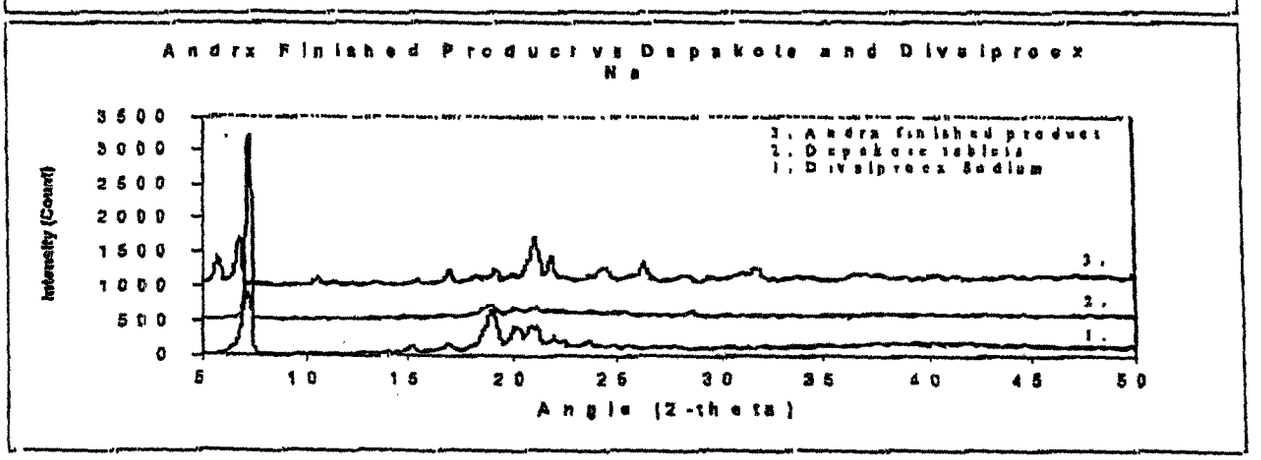
Sample[a]	Weight Gain (%) @ RT/ 80% RH[b]							
	30 min	45 min	60 min	90 min	2 hr	4 hr	6 hr	24 hr
Andrx Core Tablets (Lot # 181R001)	1.46	2.28	3.35	4.55	5.66	8.46	10.24	24.47
Andrx Finished Product (Lot # 184R001)	0.16	0.19	0.21	0.30	0.34	0.53	0.75	2.52
Depakote[7] Tablets, 500 mg (Lot # 45-404-AA-21)	0.06	0.07	0.09	0.13	0.18	0.28	0.40	1.38

a. Samples were used as is.
b. Data were calculated based on n = 2 (duplicate).

5. Results of X-ray Powder Diffraction Studies

No.	Sample	Diffraction Peak (E/ 2θ)
1	Andrx Granulation (Lot # 171R001)	5.9, 7.0, 17.2, 19.3, 21.3, 22.0, 24.7, 26.6, 32.0
2	Andrx Core Tablets (Lot # 181R001)	5.8, 6.9, 16.9, 19.3, 21.2, 21.9, 24.5, 26.4, 31.9
3	Andrx Finished Product, 500 mg (Lot # 184R001)	5.8, 6.8, 17.1, 19.2, 21.1, 21.9, 24.5, 26.4, 31.9
4	Depakote[7] Tablets, 500 mg (Lot # 45-404-AA-21)	7.2, 19.1, 21.2
5	Divalproex Sodium (Lot # 9902044)	7.3, 19.2, 20.4, 21.2
6	Sodium Valproate (Lot # 9809016)	5.6, 6.7, 16.9, 20.9, 21.8, 24.4, 26.2, 31.9





Appendix

Copies of U.S. Patent Nos.

4,988,731
5,212,326

United States Patent [19]

Meade

[11] Patent Number: 4,988,731

[45] Date of Patent: Jan. 29, 1991

[54] SODIUM HYDROGEN DIVALPROATE OLIGOMER

[75] Inventor: Edwin M. Meade, Duncan, Canada

[73] Assignee: Abbott Laboratories, Abbott Park, Ill.

[21] Appl. No.: 117,945

[22] Filed: Nov. 9, 1987

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 68,284, Aug. 20, 1979, abandoned.

[51] Int. Cl.[5] A61K 31/00; C07C 53/128

[52] U.S. Cl. 514/557; 562/606

[58] Field of Search 562/606; 514/557

[56] References Cited

U.S. PATENT DOCUMENTS

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4,127,604	11/1978	Chignac et al.	562/606
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FOREIGN PATENT DOCUMENTS

1074978	10/1954	France	562/606
2442M	4/1964	France	562/606

OTHER PUBLICATIONS

"The Pharmacological Studies on Sodium Dipropylacetate Anticonvulsant Activities and General Pharmalogical Actions", K. Shuto and T. Nishigaki, Applied Pharmacology, 4[6], pp. 937–949 (1970).

Primary Examiner—Vivian Garner

Attorney, Agent, or Firm—Steven F. Weinstock

[57] ABSTRACT

This invention concerns certain diethyl- or dipropylacetic acid salts of sodium valproate which have physiological properties similar to those of valproic acid or sodium valproate but show highly superior stability characteristics.

2 Claims, No Drawings

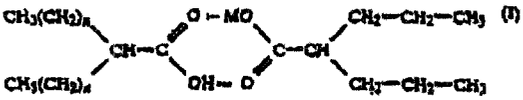
SODIUM HYDROGEN DIVALPROATE OLIGOMER

This is a continuation-in-part of copending application Serial No. 68,284, filed Aug. 20, 1979 now abandoned.

This invention relates to salts of valproic acid. In the last decade, 2-propylpentanoic acid and its alkali or earth alkali salts (hereinafter referred to as valproic acid and valproates or valproate salts, respectively) have been introduced in the artenal of drugs useful for treating epileptic seizures or convulsions. Most commonly used are valproic acid itself or its sodium salt. The former is a liquid and as such is less desirable for preparing an oral dosage form while the latter is a solid that has poor stability characteristics partially due to pronounced hygroscopicity.

It has now been found that a highly stable, nonhygroscopic, solid entity can be prepared from valproic acid and its salts, representing a single chemical molecule with welldefined physical characteristics.

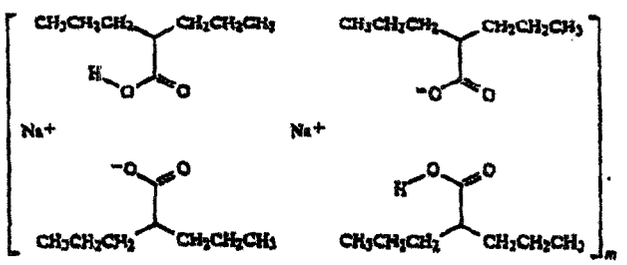
The new compound represents a single crystalline entity consisting of one molecule each of valproic acid or diethylacetic and a sodium valproate salt. There has been some uncertainty as to the structure of the compound. It was first hypothesized that the compound formed a complex in the form of a compound thus:



(I)

where M represented Na and n is 1 or 2.

Subsequent investigations have confirmed that the compound consists of one molecule each of valproic acid or diethylacetic acid and sodium valproate. However, it has been found that the molecules are distributed as an ionic oligomer, rather than as a dimer as originally believed. Thus, the sodium salt may be illustrated:



(II)

wherein m is about 2.

As can be seen from the foregoing structure, one mole each of the valproic acid moieties form coordinate bonds with the sodium of the sodium valproate molecule, and the valproate ion is ionically bonded to the sodium atom. The structure is thus consistent with the unique characteristics of the compound.

In the simplest embodiment, the above compound is prepared by dissolving one mole each of $[Me(CH_2)_n]_2$—CHCOOH and sodium valproate in 1000 ml of acetone at about 50° C. After cooling the solution to 0° C. or below, the formed new compound is filtered, washed if desired with pre-cooled acetone, and dried under reduced pressure to remove all traces of acetone. Alternately, the new compound wherein n=2 can be made in a two-component liquid medium which includes acetone. In this instance, sodium valproate is formed in situ by adding NaOH at a level of one half of a molecular equivalent of the valproic acid present, preferably as a solution in an acetone-miscible solvent for said NaOH, e.g. water. The new compound can be recovered from the liquid phase by evaporating the solvent(s) and, if desired, the new compound can be recrystallized, for instance from acetone/water, from acetonitrile or others, or the material may be spray-dried, lyophilized or purified by chromatography.

The new compound represents a single chemical molecule as can be determined by microanalysis, nmr spectrum, mixed melting point determination, IR spectrum and/or X-ray diffraction. The new compound does not have the aforementioned detrimental physical characteristics of either of the two starting materials; it is a crystalline, stable solid. Surprisingly, such a useful compound can be made only from valproic acid and diethylacetic acid on one side of the molecule, with the sodium or salt of valproic acid. When other valproate salts are used, i.e., the potassium, ammonium or magnesium salts, the resulting compound, either does not crystallize, does not form or is highly unstable in the presence of any atmospheric moisture.

The process for making the compounds of this invention are best illustrated by reference to the following examples which, however, are not intended to limit the invention in any respect.

EXAMPLE 1

In 1000 ml of acetone at about 50° C. is dissolved 166 g of sodium valproate and 144 g of valproic acid. The solution is cooled to about 0° C., filtered and the crystalline precipitate is washed with pre-cooled acetone at about 0° C. The new compound is obtained in a yield of 90% of theory. Additional material can be obtained by using the acetone filtrate in a subsequent batch.

The new material is a stable, white, crystalline powder which melts at 98–100° C. Its moisture stability is established by placing samples of the material for 45 minutes in a controlled environment at room temperature and 80% relative humidity. No weight gain is observed, while under the same condition, the simple sodium salt of valproic acid gains between 17 and 24% in weight.

The infrared spectrum is consistent with proposed structure II and has the following characterizing absorption bands: strong bands at 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1}. The first two of these indicate the various methyl groups, the last two are due respectively to the antisymmetric and symmetric O—C—O—stretching vibrations of the carboxyl salt. The remaining

strong bands indicate the stretching vibrations of the various methylene groups and the C=O in the carboxylic acid group. while the weak, broad bands at 2450 and 1900 cm^{-1} are due to intramolecularly bounded OH groups of the carboxylic acid.

EXAMPLE 2

In the fashion of Example 1 but using sodium valproate with the molar equivalents of dibutylacetic acid or diethylacetic acid, respectively, the corresponding hydrogen sodium mixed salts of the assumed structure II with n=b 3 or 1, respectively, are obtained. In the instance of dibutylacetic acid, a very hygroscopic product is obtained which is very difficult to handle and therefore unsuitable for pharmaceutical dosage forms. The mixed salt obtained with diethylacetic acid is a white crystalline powder which is stable to ordinary storage conditions and essentially nonhygroscopic.

EXAMPLE 3

In a comparison of anticonvulsant activities of
A: valproic acid (stable, liquid)
B: sodium valproate (hygroscopic solid)
C: compound (stable solid) of Example 1
the oral ED50 based on equimolar valproic acid equivalents are established by standard procedures. The results are as follows:

	A	B	C
Audiogenic seizures (mice)	156	161	81 mg/kg
Pentylenetetrazole seizures (mice)	<800	282	178 mg/kg
Pentylenetetrazole seizures (rats)	359	415	362 mg/kg

In a bioavailability study carried out with (A) and (C) above in various animal species, the peak blood plasma levels of oral, equimolar doses are determined according to standard procedures, 30 minutes after drug administration.

	A	C
Mouse (200 mg/kg)	133.7	307.4 mg/kg
Rat (200 mg/kg)	84.1	63.0 mg/kg
Dog (25 mg/kg)	65.2	73.6 mg/kg
Dog (25 mg/kg) AUC*	82.3	95.0 hr · mcg/ml

*Area under the curve value for 0-7 hours.

From the above examples, it will be seen that the new material has equal or better physiological properties than either valproic acid or sodium valproate. Since the new compound has far superior physical characteristics than either "monomer" from which it is made, it greatly facilitates the preparation of solid pharmaceutical dosage forms, and specific amounts can be weighed out and blended with starch and/or other binders to form a flowable powder which can be forwarded to standard tableting machines after granulation. Neither the hygroscopic sodium salt of valproic acid nor the liquid valproic acid itself can be processed in this fashion without special precautions or absorbents.

The new compounds can be tableted in accordance with Example XIII of U.S. Pat. No. 3,325,361 and analogous methods. In these procedures, one or more diluents and/or excipients are used, e.g., starch, talcum powder, lubricants, disintegrators, flavoring agents, coloring agents and the like. These additives, of course, are the usual pharmaceutically acceptable carriers or diluents employed in routine fashion by tablet formulators.

The above structure II is the most likely true two-dimensional view of the sodium/hydrogen divalproate and seems to be confirmed by IR and nmr spectra, by molecular weight and microanalytic values. Thus, the new material should be characterized not by depicting a structural formula but by reference to a single compound of formula $(CH_3CH_2CH_2)_2CHCO_2Na/R_2CHCO_2H$ or $[(R_2CHCO_2)(R_2CHCO_2)]Na.H$ wherein each R is propyl, or by reference to sodium/hydrogen divalproate.

It will be understood that various changes and modifications can be made in the details of procedure, formulation and use without departing from the spirit of the invention, especially as defined in the following claims.

I claim:

1. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 4 such units.

2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 4 such units.

* * * * *

US005212326A

United States Patent [19]

Meade

[11] Patent Number: 5,212,326

[45] Date of Patent: * May 18, 1993

[54] SODIUM HYDROGEN DIVALPROATE OLIGOMER

[75] Inventor: Edwin M. Meade, Duncan, Canada

[73] Assignee: Abbott Laboratories, Abbott Park, Ill.

[*] Notice: The portion of the term of this patent subsequent to Jan. 29, 2008 has been disclaimed.

[21] Appl. No.: 637,828

[22] Filed: Jan. 7, 1991

Related U.S. Application Data

[63] Continuation of Ser. No. 117,945, Nov. 9, 1987, Pat. No. 4,988,731, which is a continuation of Ser. No. 545,719, Oct. 26, 1983, abandoned, which is a continuation-in-part of Ser. No. 65,284, Aug. 20, 1979, abandoned.

[51] Int. Cl.[5] C07B 53/00; A01N 37/00; A61K 31/19

[52] U.S. Cl. 562/606

[58] Field of Search 562/606; 514/557

[56] References Cited

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Primary Examiner—José G. Dees
Assistant Examiner—Joseph M. Conrad
Attorney, Agent, or Firm—Steven F. Weinstock

[57] ABSTRACT

This invention concerns certain diethyl- or dipropylacetic acid salts of sodium valproate which have physiological properties similar to those of valproic acid or sodium valproate but show highly superior stability characteristics.

5 Claims, No Drawings

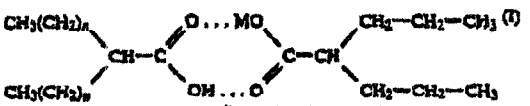
SODIUM HYDROGEN DIVALPROATE OLIGOMER

This application is a continuation of Ser. No. 117,945, filed Nov. 9, 1987, now U.S. Pat. No. 4,988,731 issued Jan. 29, 1991, which is a continuation of Ser. No. 545,719 filed Oct. 26, 1983, now abandoned, which is a continuation-in-part of Ser. No. 068,284 filed Aug. 20, 1979, now abandoned.

This invention relates to salts of valproic acid. In the last decade, 2-propylpentanoic acid and its alkali or earth alkali salts (hereinafter referred to as valproic acid and valproates or valproate salts, respectively) have been introduced in the arsenal of drugs useful for treating epileptic seizures or convulsions. Most commonly used are valproic acid itself or its sodium salt. The former is a liquid and as such is less desirable for preparing an oral dosage from while the latter is a solid that has poor stability characteristics partially due to pronounced hygroscopicity.

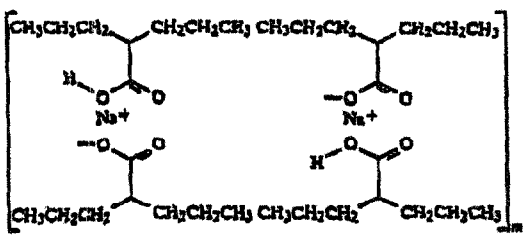
It has now been found that a highly stable, nonhygroscopic, solid entity can be prepared from valproic acid and its salts, representing a single chemical molecule with welldefined physical characteristics.

The new compound represents a single crystalline entity consisting of one molecule each of valproic acid or diethylacetic and a sodium valproate salt. There has been some uncertainty as to the structure of the compound. It was first hypothesized that the compound formed a complex in the form of a compound thus:



where M represented Na and n is 1 or 2.

Subsequent investigations have confirmed that the compound consists of one molecule each of valproic acid or diethylacetic acid and sodium valproate. However, it has been found that the molecules are distributed as an ionic oligomer, rather than as a dimer as originally believed. Thus, the sodium salt may be illustrated:



wherein m is about 2 to 3.

As can be seen from the foregoing structure, one mole each of the valproic acid moieties form coordinate bonds with the sodium of the sodium valproate molecule, and the valproate ion is ionically bonded to the sodium atom. The structure is thus consistent with the unique characteristics of the compound.

In the simplest embodiment, the above compound is prepared by dissolving one mole each of $[Me(CH_2)_n]_2$-CHCOOH and sodium valproate in 1000 ml of acetone at about 50° C. After cooling the solution to 0° C. or below, the formed new compound is filtered, washed if desired with pre-cooled acetone, and dried under reduced pressure to remove all traces of acetone. Alternately, the new compound wherein n=2 can be made in a two-component liquid medium which includes acetone. In this instance, sodium valproate is formed in situ by adding NaOH at a level of one half of a molecular equivalent of the valproic acid present, preferably as a solution in an acetone-miscible solvent for said NaOH, e.g. water. The new compound can be recovered from the liquid phase by evaporating the solvent(s) and, if desired, the new compound can be recrystallized, for instance from acetone/water, from acetonitrile or others, or the material may be spray-dried, lyophilized or purified by chromatography.

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It will be understood that various changes and modifications can be made in the details of procedure, formulation and use without departing from the spirit of the invention, especially as defined in the following claims.

I claim:

1. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 4 to 6 such units.

2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 4 to 6 such units.

3. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 6 such units.

4. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 6 such units.

5. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and having physical/chemical properties as follows:

a. stable, white crystalline powder;

b. melting point of 98°–100° C.; and

c. an infrared spectrum having strong absorption bands at about 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1}.

* * * * *